Complete Summary

GUIDELINE TITLE

Idiopathic membranous nephropathy: use of other therapies.

BIBLIOGRAPHIC SOURCE(S)

Thomas M. Idiopathic membranous nephropathy: use of other therapies. Nephrology 2006 Apr;11(S1):S172-4.

Thomas M. Idiopathic membranous nephropathy: use of other therapies. Westmead NSW (Australia): CARI - Caring for Australians with Renal Impairment; 2005 Sep. 6 p. [17 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Chronic kidney diseases
- Idiopathic membranous glomerulonephritis

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Nephrology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the available clinical evidence pertaining to the impact of specific interventions not covered in other guidelines on declining renal function in chronic kidney disease patients with idiopathic membranous glomerulonephritis

TARGET POPULATION

Adults and children with idiopathic membranous glomerulonephritis

INTERVENTIONS AND PRACTICES CONSIDERED

Second-line therapy with azathioprine with corticosteroids, intravenous immunoglobulin, fludarabine, mycophenolate mofetil, and monoclonal antibodies was considered but not recommended.

MAJOR OUTCOMES CONSIDERED

- Remission of membranous glomerulonephritis
- Reduction in proteinuria

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Databases searched: Medical Subject Heading (MeSH) terms and text words for Membranous Nephropathy were combined with MeSh terms and text words for azathioprine, immunoglobulin, fludarabine, mycophenolate mofetil and rituximab. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for trials in membranous nephropathy not indexed in Medline.

Date of searches: 9 September 2004.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Level I: Evidence obtained from a systematic review of all relevant randomized controlled trials (RCTs)

Level II: Evidence obtained from at least one properly designed RCT

Level III: Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method); comparative studies with concurrent controls and allocation not randomized, cohort studies, case-control studies, interrupted time series with a control group; comparative studies with historical control, two or more single arm studies, interrupted time series without a parallel control group

Level IV: Evidence obtained from case series, either post-test or pretest/post-test

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Recommendations of Others. Recommendations regarding use of azathioprine, immunoglobulin, fludarabine, mycophenolate mofetil, and monoclonal antibodies in the treatment of idiopathic membranous nephropathy from the following groups were discussed: Kidney Disease Outcomes Quality Initiative, UK Renal Association, Canadian Society of Nephrology, European Best Practice Guidelines, and International Guidelines.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the levels of evidence (I–IV) can be found at the end of the "Major Recommendations" field.

Guidelines

No recommendations possible based on Level I or II evidence

Suggestions for Clinical Care

(Suggestions are based on Level III and IV evidence)

- While there have been mixed reports of success with a number of agents, further evidence is required before they can be recommended as second line therapy in membranous glomerulonephritis (MGN).

Azathioprine

Studies in the treatment of idiopathic MGN have found mixed benefits from using azathioprine combined with corticosteroids over steroid alone.

- One study demonstrated that the addition of oral azathioprine to a regimen of intravenous pulse methylprednisolone and oral prednisone could reverse or stabilize progressive kidney failure in patients with membranous nephropathy.

Most series have not shown any benefit.

- In a small controlled trial, five patients with the nephrotic syndrome due to idiopathic MGN received azathioprine, 2.5 mg/kg/d, while four others received placebo. After 1 year of treatment there was no significant difference in creatinine clearance or 24-hour excretion of protein between the two groups.
- The Sheffield Kidney Institute reviewed 58 patients with idiopathic MGN and nephrotic-range proteinuria. Thirty-eight patients were treated with

prednisolone (1 mg/kg/d) and azathioprine (2 mg/kg/d) for a median period of 26 months. Twenty patients received no specific treatment for MGN and served as a control group. Neither the level of proteinuria, the rate of renal decline nor the proportion of patients with deteriorating renal function differed significantly between the groups. In addition, adverse effects of immunosuppressive treatment were observed in 9 patients.

Immunoglobulin

Pooled intravenous immunoglobulin (IgG) in a few small series has been shown to reduce proteinuria and stabilize renal function in patients with resistant nephrotic syndrome [Level III evidence, single study, additional selected case series].

- One study followed 9 patients with idiopathic MGN following treatment with pulse doses of IgG (0.4 g/kg body weight) for 3 consecutive days, repeated 3 times at 21-day intervals for 10 months. In 5 patients, a complete remission of proteinuria (daily proteinuria less than 0.2 g) was observed, and 3 patients showed partial remission (proteinuria 2 g/day). In responder patients, clinical and biological findings of the nephrotic syndrome disappeared and a statistically significant increase of creatinine clearance was observed.
- Another study reviewed 86 patients with primary MGN for at least 5 years. They treated 30 of these patients with 1–3 short-term courses of low-dose intravenous immune globulin (5–10 g/day) [100–150 mg/kg/day] for 6 consecutive days. There was no difference in the long-term outcome in patients treated with intravenous immunoglobulin therapy compared with patients not receiving therapy with immunoglobulin. A subgroup of patients with 'homogenous type MGN with electron microscopy findings of synchronous electron-dense deposits' had earlier induction of remission.

Fludarabine

Fludarabine has been reported to lead to remission in some patients with MGN (Level IV evidence, anecdotal reports).

- Treatment of refractory chronic lymphocytic leukaemia (CLL) with fludarabine, a purine nucleoside analogue, has been associated with remission of malignancy-associated MGN.
- In one study, the investigators treated 7 patients with refractory idiopathic membranous nephropathy with 6-monthly cycles of fludarabine. Although all patients developed significant lymphopenia, proteinuria decreased by > 50% in 5 of 7 patients ($P = 0.11$) and glomerular filtration rate (GFR) improved in all those with renal failure at baseline.

Mycophenolate mofetil

Mycophenolate appears to reduce proteinuria in some patients with resistant MGN (Level IV evidence, small case series, variable results).

- One study treated 18 patients with refractory MGN, 13 of whom achieved remission on 1.0–2.0 g/d for 3–6 months.

- One study treated 16 nephrotic patients with MGN with mycophenolate mofetil. Fifteen patients had steroid-resistant disease; cytotoxic agents had failed in 6 patients and cyclosporin therapy had failed in 5 patients. Six patients experienced a halving of proteinuria, which occurred after a mean duration of 6 months of therapy. Partial remissions occurred in 2 patients. There were no significant changes in mean values for serum creatinine during the study.
- One study also described reductions in proteinuria and stabilising of creatinine in 3 patients with MGN.
- One group of investigators studied 17 patients with MGN including 15 with nephrotic range proteinuria and 6 with renal insufficiency. Indications for mycophenolate mofetil treatment were steroid- (11/17), cyclosporine- (4/17) or cytotoxic (1/17) dependency. After 5-12 months of follow-up, there was a 61.1% reduction in protein excretion. Two patients (13.3%), both of whom were nephrotic, achieved a complete remission; 8 patients (60%), all of whom were nephrotic, achieved a partial remission; and 2 patients (13.3%), including 1 nephrotic, had increased proteinuria. Eight of the 15 (53.3%) nephrotic patients improved to sub-nephrotic proteinuria with treatment. Two patients relapsed after mycophenolate mofetil was stopped, and they both responded to re-treatment. Three of 6 patients with renal insufficiency experienced substantial improvement in excretory renal function.
- One study gave mycophenolate mofetil 2 g/day for 9 months to 8 patients with stage III–IV idiopathic membranous nephropathy. Previous treatment had failed in 5 of 8 patients (three patients had received cyclosporin and steroids, one cyclosporin, steroids and cyclophosphamide and one an alternative use of steroids and chlorambucil). Proteinuria decreased significantly during the treatment ($P < 0.05$), from 4.4 g/d at the start, to 2.0 g/day after 3 months, and 1.9 g/day after 6 months and 9 months. Renal function improved slightly, but not significantly ($P > 0.05$).

Monoclonal antibodies

Monoclonal antibodies against the cell surface antigen CD20 of B cells may reduce proteinuria in some patients with idiopathic MGN.

- One study followed 8 patients with idiopathic MGN and long-lasting persistent proteinuria, following an intravenous infusion of the anti-CD20 monoclonal antibody, rituximab. After 20 weeks of treatment, there was a 60% reduction in urinary proteinuria. At 12 months, proteinuria decreased to $\leq$ 0.5 g/24 h or $\leq$ 3.5 g/24 h in two and three patients, respectively. There was no significant loss of renal function in any patient.
- Eculizumab, a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its proinflammatory elements, did not appear to have any significant effect on proteinuria or renal function in patients with membranous nephropathy, although this Phase II study was not designed to test this outcome and the dose required for efficacy testing may not have been achieved.

Definitions:

Levels of Evidence

Level I: Evidence obtained from a systematic review of all relevant randomized controlled trials (RCTs)

Level II: Evidence obtained from at least one properly designed RCT

Level III: Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method); comparative studies with concurrent controls and allocation not randomized, cohort studies, case-control studies, interrupted time series with a control group; comparative studies with historical control, two or more single arm studies, interrupted time series without a parallel control group

Level IV: Evidence obtained from case series, either post-test or pretest/post-test

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of patients with idiopathic membranous glomerulonephritis

POTENTIAL HARMS

Side effects of treatment

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Thomas M. Idiopathic membranous nephropathy: use of other therapies. Nephrology 2006 Apr;11(S1):S172-4.

Thomas M. Idiopathic membranous nephropathy: use of other therapies. Westmead NSW (Australia): CARI - Caring for Australians with Renal Impairment; 2005 Sep. 6 p. [17 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Apr

GUIDELINE DEVELOPER(S)

Caring for Australasians with Renal Impairment - Disease Specific Society

SOURCE(S) OF FUNDING

Industry-sponsored funding administered through Kidney Health Australia

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Merlin Thomas

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All guideline writers are required to fill out a declaration of conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Caring for Australasians with Renal Impairment Web site.

Print copies: Available from Caring for Australasians with Renal Impairment, Locked Bag 4001, Centre for Kidney Research, Westmead NSW, Australia 2145

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- The CARI guidelines. A guide for writers. Caring for Australasians with Renal Impairment. 2006 May. 6 p.

Electronic copies: Available from the Caring for Australasians with Renal Impairment (CARI) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on May 8, 2008.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and

related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 5/25/2009